

EDITORIAL COMMENT

Transcatheter Aortic Valve Replacement

Lessons Gained From Extreme-Risk Patients*



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Percutaneous coronary intervention (PCI) and transcatheter aortic valve replacement (TAVR) have started at the antipodes of the risk spectrum. Although the former was established in low-risk patients and later adopted in higher risk subsets with increasing experience, TAVR was first introduced among inoperable patients before extending experience to patients who were surgical candidates. Despite the prohibitive risk profile of inoperable patients owing to comorbidities and the procedure being in its infancy, TAVR demonstrated a robust survival benefit compared with conservative management, and the procedural risk was offset by the spontaneous course of the disease, underlining the malignant course of patients with severe aortic stenosis if untreated (1,2). Of note, it is critical to differentiate between extreme-risk interventions on the one hand and futile interventions on the other.

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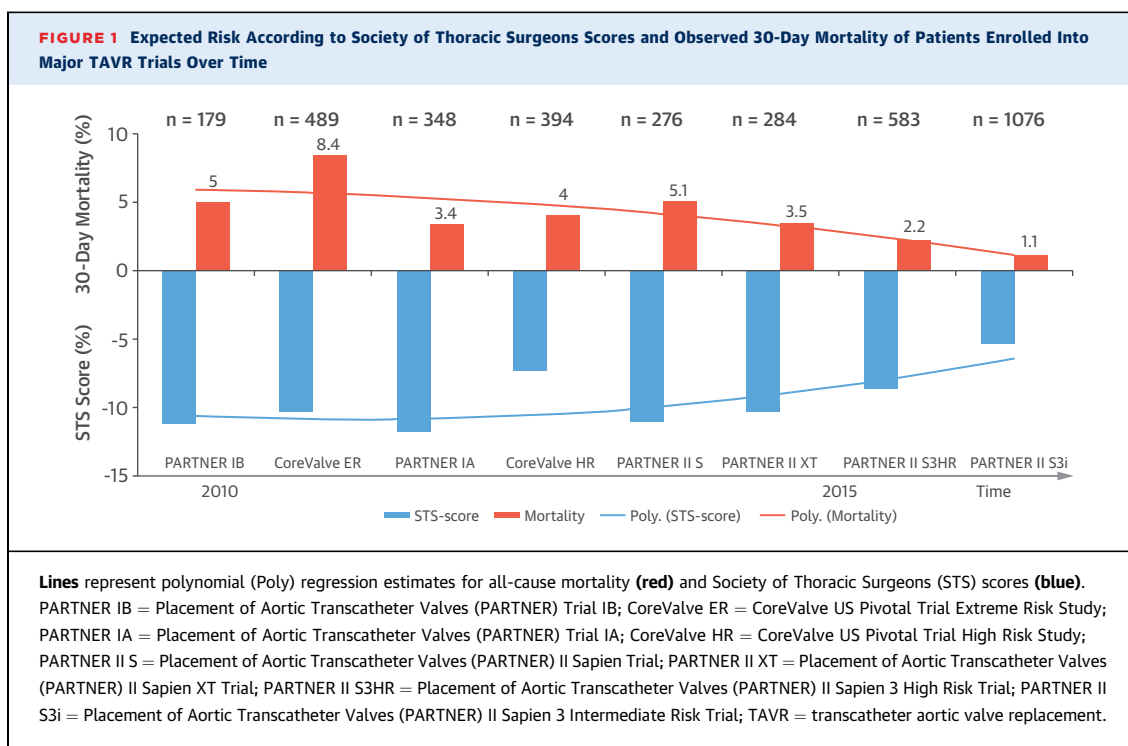
TAVR is considered futile in patients with an estimated life expectancy of <1 year and in patients in whom comorbidities preclude the expected benefit from correction of aortic stenosis in terms of survival, symptom relief, and quality of life. The encouraging results in patients at highest risk subsequently propelled research to investigate the safety and efficacy of TAVR among patients at high to intermediate surgical risk (Figure 1).

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In this issue of the *Journal*, Yakubov et al. (3) report the 2-year clinical outcomes after TAVR with the self-expanding valve prosthesis (CoreValve, Medtronic, Minneapolis, Minnesota) among patients with severe aortic stenosis deemed at extreme risk for surgical aortic valve replacement (SAVR). A total of 489 patients from 41 centers considered to have $\geq 50\%$ mortality or irreversible morbidity at 30 days in case of SAVR as evaluated by an interdisciplinary heart team underwent transfemoral TAVR. Throughout 2 years of follow-up, rates of all-cause mortality, cardiovascular mortality, and major stroke were 36.5%, 26.6%, and 5.1%, respectively. Incremental rates of adverse events between the first and second years of 12.3% for all-cause mortality, 7.9% for cardiovascular mortality, and 0.8% for major stroke reflect the burden of comorbidities and limited life expectancy in this elderly study population, whereas improvement in the aortic valve effective orifice area, reduction in transvalvular gradient, and improvement in functional class was sustained.

All-cause mortality in the present study was comparable to the 2-year event rates observed in PARTNER (Placement of Aortic Transcatheter Valves) Trial 1B (43%) and PARTNER Trial 1A (34%), and Society of Thoracic Surgeons scores $>15\%$ tended to be predictive of 2-year mortality in the present analysis. However, 5-year data from the PARTNER 1B study suggested benefit in favor of TAVR even in the subset of patients with Society of Thoracic Surgeons scores $>15\%$ compared with conservative management. Measures of frailty as well as need for assisted living may be clinically more meaningful and predictive than risk scales developed for conventional SAVR to identify patients who may no longer be candidates for an intervention in the patient population under discussion (4,5). The findings of the extreme-risk study with the self-expandable valve, as well as the PARTNER 1B, suggest that conservative management should be limited to patients with palliative



conditions, whereas additional efforts should aim to fully exploit adequate access of extreme- and high-risk patient populations to TAVR.

Among patients deemed inoperable, all-cause mortality as high as 72% has been reported in the PARTNER 1B study at 5 years and 38% in the present study at 2 years, whereas structural valve deterioration is rare in this patient population (<3% in survivors) (1,2,6,7). The discrepancy between rather low rates of prosthesis deterioration and high rates of clinical adverse events highlights the critical impact of patient comorbid conditions in studies evaluating TAVR among extreme- and high-risk populations. Of note, survivorship bias may distort evidence of TAVR outcomes in 2 ways. On the one hand, early death unrelated to aortic stenosis but due to comorbidities may limit the benefits of TAVR in some patients. On the other hand, the adverse clinical course determined by comorbidities may camouflage the clinical detection of valve-related adverse outcomes, which could emerge during longer-term follow-up. In this context, paravalvular regurgitation amounted to 10.7% at discharge, but was unchanged between 1 and 2 years, at 4.3% and 4.4%, respectively, in the present study. Although a paired analysis of echocardiographic findings at discharge and 1-year follow-up in 29 patients suggests remodeling of the annular-bioprostheses interface as a potential explanation for the lower rate of paravalvular

regurgitation during follow-up after self-expandable valve implantation, attrition bias due to premature death cannot be excluded. This is important as moderate and severe paravalvular regurgitation has been consistently reported as a predictor of mortality after TAVR and constitutes the most important barrier to extending the procedure to lower-risk patients (8). Conversely, the stable transvalvular aortic valve gradient and effective orifice area throughout 2 years of follow-up in the present study are notable. These findings are in line with recent data of the PARTNER 1A Trial suggesting similar valve performance for transcatheter and surgical bioprostheses throughout 5 years of follow-up and address concerns regarding valve durability (6). In addition, hemodynamic measurements after TAVR suggest larger effective aortic valve area and lower transvalvular gradient compared with SAVR (9), hence reducing the incidence of patient prosthesis mismatch (10). This finding appears pronounced with use of the self-expandable prosthesis and may be of particular importance in patients with small valve anatomy compared with SAVR (11).

Inevitably, the findings of the present analysis are of somewhat historical value due to recent device iterations. Technical refinements of newer-generation transcatheter bioprostheses successfully minimize the risk of paravalvular aortic regurgitation by means of circumferential skirts at the valvular inflow

site, mitigate the risk of vascular access site and bleeding complications due to lower profile delivery catheters, and reduce the risk of atrioventricular conductance disturbances related to more precise positioning within the annulus. Outcomes based on recent iterations of balloon-expandable and repositional transcatheter valve systems have reported significant improvements, with rates of paravalvular aortic regurgitation mimicking results of SAVR and very low rates of periprocedural mortality (12,13) (Figure 1).

Presence of coronary artery disease was predictive of all-cause mortality at 2 years in the present analysis. Available observational data on the impact of coronary artery disease on clinical outcomes among patients undergoing TAVR are equivocal and limited by the small sample size, relatively short duration of follow-up, substantial heterogeneity in terms of anatomic and physiological extent of coronary artery disease, and selection bias introduced by revascularization (14). Of note, patients with previous PCI/coronary artery bypass grafting and those in need for revascularization were excluded from participation in the present study. Notwithstanding, more advanced coronary artery disease (SYNTAX score >22) and extent of ischemia may be associated with adverse clinical outcome after correction of aortic stenosis and requires careful consideration in therapeutic decision making (14,15).

The risk of thromboembolic cerebrovascular accidents is greatest within the first hours after TAVR and is a function of patient age, severity of aortic valve stenosis, extent of aortic arch atheroma, post-valve deployment balloon dilation, and repeated prosthesis placement (16). The optimal type and duration of antithrombotic and antiplatelet treatment after TAVR remain to be defined as well as the role of dedicated cerebral protection devices (17,18). In the present study, the risk of stroke was 8.6% at 2 years and rather stable between 1 and 2 years of follow-up. Moreover, recent data from the CoreValve US Pivotal Trial High Risk Study demonstrate a trend toward a lower risk of stroke after TAVR compared with SAVR (11).

Atrioventricular conductance disturbances with the need for permanent pacemaker (PPM) implantation occur more frequently with self-expandable

compared with balloon-expandable prostheses. In the present study, the rate of PPM implantation was 22% at 30 days, 26% at 1 year, and 29% at 2 years. The most important predictors of PPM implantation include intraoperative atrioventricular block, right bundle branch block, implantation of a self-expandable TAVR prosthesis, left anterior hemiblock, first-degree atrioventricular block, and male sex (19). However, PPM implantation has not been associated with adverse clinical outcome after TAVR so far, and device iterations aiming at more precise positioning of the prosthesis within the annulus may further mitigate the frequency of this adverse event (20).

In summary, TAVR in extreme-risk patients not only improves survival but has pronounced effects on quality of life, symptom and functional status as well as cognitive function. With a number needed to treat of <5 to prevent 1 death among inoperable patients, TAVR has resulted in a paradigm shift in the treatment of patients with severe aortic stenosis. In line with recent guidelines on valvular heart disease in Europe and the United States, TAVR has become the standard of care in inoperable patients (Class IB) and a valuable alternative to SAVR among high-risk patients (Class IIaB) (21,22). Challenges to be addressed in the future will be to improve education and timely access to medical care as well as adequate reimbursement. Although evidence from randomized clinical trials suggests similar or superior outcomes of TAVR compared with SAVR among high- and intermediate-risk patients with severe aortic stenosis (6,9,11), the ongoing refinement of the procedure and TAVR prostheses will catalyze research among lower-risk patients. The expansion of TAVR to lower-risk patients further raises the bar in terms of outcomes and shifts the focus beyond patient-related to prosthesis-related outcomes. Although TAVR has started at the extreme end of the risk spectrum, it has the potential to mature into a procedure for all patients with severe aortic stenosis, irrespective of risk, in the future.

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